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(54) Title: SECRETIN AND SECRETIN PHARMACEUTICALS FOR TREATING ATTENTION DEFICIT DISORDER

(57) Abstract: A method for treating Attention Deficit Disorder or alleviating symptoms thereof wherein the hormone secretin, or an acceptable pharmaceutical synthetic thereof, is administered to a person suffering from the syndrome or its symptoms. Patients so treated exhibit greatly improved concentration and performance over time, and their symptoms, including distractibility, impulsivity, hyperactivity, difficulty in following directions, mental fatigue and confusion, are greatly alleviated.

SECRETIN AND SECRETIN PHARMACEUTICALS FOR TREATING ATTENTION DEFICIT DISORDER

BACKGROUND OF THE INVENTION

1. FIELD OF THE INVENTION

The invention relates to a pharmaceutical and a method for treating Attention Deficit Disorder and alleviating the symptoms thereof. More particularly, the invention relates to the use of the hormone secretin, or an acceptable pharmaceutical synthetic thereof, in the treatment of Attention Deficit Disorder.

2. DESCRIPTION OF RELATED ART

Attention Deficit Disorder is a neurological syndrome characterized by distractibility and impulsivity. These symptoms are often accompanied by one or more other symptoms, including hyperactivity, difficulty in following directions, mental fatigue, confusion, low stress tolerance with emotional over-reaction to the stress, poor organization with poor task completion, wide mood swings, short or excessive temper, aggressiveness and/or periodic depression. This syndrome has been variously referred to as Minimal Brain Dysfunction, Hyperactivity-Impulsivity, Attention Deficit Disorder, Undifferentiated-Attention-Deficit Disorder and Attention-Deficit Hyperactivity Disorder. Attention-Deficit

Hyperactivity Disorder is the official term for this syndrome used by the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association. This term incorporates the symptom of hyperactivity, although hyperactivity may not be present. The syndrome will hereinafter be referred to as "Attention Deficit Disorder" or its acronym, "ADD," and said references will include both those persons who exhibit the symptom of hyperactivity and those who do not.

According to published statistics, approximately 3 to 10 percent of the population is affected by ADD. However, many clinicians believe that it is more likely that two to three times this number suffer from varying degrees and intensities of this syndrome. It was originally believed that ADD was a disorder of childhood alone, and that the disorder would be outgrown during adolescence. It is now known that a large percentage of those affected by this disorder (roughly between a third to two-thirds of the ADD population) will continue to have ADD throughout adulthood.

Although the cause of this syndrome has not yet been clinically proven, most clinicians and researchers believe that ADD is biologically inherited and results from a neurochemical imbalance. There are millions of neurons, or nerve cells, in the brain that store information and are responsible for relaying information. Each neuron may connect to as many as 10,000 other nerve cells. Neurons use electricity to transmit information down the length of their own cell structure, repeating the process with neurons to which they are connected. However, because a microscopic gap, called a synapse, exists between each of the neurons, neurons must rely on chemicals or

molecules in the brain, referred to as "neurotransmitters," to signal the connecting neurons and to relay information from one neuron to another.

Neurotransmitters are therefore the means by which neurons activate other neurons and communicate with each other. When there are inadequate amounts of neurotransmitters to signal other neurons, various brain circuits may become under- or overactive due to lack of communication between nerve cells. It is widely believed that ADD results from a failure, or an insufficient supply, of one or more of the dozen or so major brain neurotransmitters that are responsible for activating and relaying information between the millions of neurons in the brain.

Currently, the predominate means of treating ADD is through the use of two main classes of medication: stimulants and antidepressants. The use of these medications recognizes that ADD results from a failure of one or more of the major neurotransmitters. Stimulants are used to act on or replace the failed neurotransmitter(s) to activate or stimulate the central nervous system. The most common stimulants currently used in the treatment of ADD include Ritalin (generic name, methylphenenidate), Dexedrine (dextroamphetamine), Adderall (amphetamine) and Cylert (pemoline). Antidepressants are used to enhance or raise the level of the failed neurotransmitter(s). The antidepressants most commonly used in the treatment of ADD are in a class called "tricyclic antidepressants," and they include Norpramin (generic name, despramine), Pamelor (nortriptyline), Tofrail (imipramine), Wellbutrin (bupropion) and Prozac (fluoxetine).

There are often side-effects from the use of these medications (i.e. stimulants and antidepressants) that are unpleasant and sometimes even dangerous. Depending on the medication used, these side-effects include overstimulation, increased irritability, depression, insomnia, skin rashes, weight loss, nausea, dizziness, drowsiness, headache, dryness of mouth, heart palpitations, elevated blood pressure, diarrhea, constipation, decrease in sexual libido and potential for liver failure. Additionally, a given medication may initially work for a patient, but then destabilize after a period of use. When this happens, the medication is no longer effective for alleviating the ADD symptoms that a particular patient experiences, and in some cases the continued use of the medication may even exacerbate the symptoms. Moreover, these medications do not treat the underlying cause of the neurochemical imbalance that results in ADD, but merely artificially replace or increase, to some degree, the levels of the neurotransmitters that are out of balance.

No treatment method currently exists for ADD that improves the body's ability to produce balanced neurotransmitters. Therefore, there is a need for a method that is effective in treating Attention Deficit Disorder by improving the body's ability to produce balanced neurotransmitters.

The invention involves a method for treating Attention Deficit Disorder wherein the hormone secretin, or an acceptable pharmaceutical synthetic thereof, is administered to a person suffering from Attention Deficit Disorder. Secretin is a polypeptide hormone containing 27 amino acids. It is produced by the endocrine cells of the upper small intestine. Secretin,

gastrin and cholecystokinin are the 3 major hormones that control human digestion. It is generally believed that the primary action of secretin is to increase the volume and bicarbonate content of secreted pancreatic juices. Secretin is released when acid chyme with pH less than 4.5 to 5.0 enters the duodenum from the stomach. When released, secretin stimulates the pancreas to emit digestive fluids that are rich in bicarbonate, which neutralizes the acidity of the intestines. It is believed that secretin also stimulates the liver to produce bile and stimulates the stomach to produce pepsin, an enzyme that aids the digestion of protein.

Secretin has been proven effective in diagnosing (as opposed to treating) impaired pancreatic function. The US Food and Drug Administration (FDA) has approved porcine secretin, extracted from the duodenum of pigs, for singly dose use in diagnosing pancreatic disorders. For these purposes, porcine derived secretin is administered by intravenous infusion during upper gastrointestinal endoscopy or other tests.

SUMMARY OF THE INVENTION

It is the object of the invention to provide a new drug and method which is effective in the treatment of Attention Deficit Disorder (ADD).

It is another object of the invention to provide a drug and method which is effective in alleviating symptoms of Attention Deficit Disorder.

In accordance with the invention, the hormone secretin, or an acceptable pharmaceutical thereof, is administered to

patients suffering from ADD or the symptoms thereof. It has been discovered that the administration of this endogenous substance as a pharmaceutical for the treatment of ADD leads to surprising therapeutic results without any adverse side-effects. In patients suffering from ADD, a clear alleviation of their symptoms, including distractibility, impulsivity, hyperactivity, difficulty in following directions, mental fatigue and confusion, is achieved.

The invention provides the only treatment method for ADD that improves the body's ability to produce balanced neurotransmitters. With this treatment method, patients need only undergo treatment on a periodic basis, and will not need to take stimulants, antidepressants or other medications having side-affects that are unpleasant and sometimes even dangerous.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the invention, the hormone secretin, or an acceptable pharmaceutical synthetic thereof, is administered to an individual suffering from Attention Deficit Disorder. The secretin, or an acceptable pharmaceutical synthetic thereof, is administered intravenously over a period of about 1 to 4 minutes at a dose of 1 CU (clinical unit) of pharmaceutically acceptable secretin per pound of body weight. The intravenous infusion is accomplished by attaching a winged infusion set, otherwise known as a "butterfly needle," to a syringe containing the secretin dosage, and by inserting the needle into the vein in the arm. The dosage is then pushed through the syringe into the bloodstream over a period of about 1 to 4 minutes.

The inventors' preferred method for performing the

intravenous infusion is to first push about 1 ml of the secretin solution into the bloodstream and then to wait 1 minute to make sure the patient is not experiencing any adverse reactions, such as the breakout of a rash or difficulty in breathing. The remainder of the solution is then pushed into the bloodstream over a period of about 2 to 3 minutes.

To date, the inventors have used porcine derived secretin in the employment of the invention. Synthetic versions of human and porcine secretin may soon be available, and it is intended that the scope of the invention would include pharmaceutically acceptable synthetics of human and porcine secretion. The scope of the invention is also intended to cover the hormone secretin derived from other mammals, and acceptable pharmaceutical synthetics thereof, if the composition of the secretin from those sources are found to be substantially the same as human or porcine secretin.

In all cases, pharmaceutically acceptable solutions of the secretin hormone, or synthetics thereof, should be used. The particular solution employed by the inventors consists of porcine secretin manufactured by Ferring AB, which contains 75 CU of lyophilized, sterile purified secretin, 1 mg of L-cysteine hydrochloride and 20 mg of mannitol per vial. The Ferring AB product comes in a powdered form, and will need to be reconstituted prior to infusion by dissolving the contents of each vial in 7.5 ml of Sodium Chloride Injection USP, to yield a concentration of 10 CU per ml.

Based on the trials conducted to date, it appears that the treatment may need to be repeated every 2 to 4 months to achieve maximum and sustained results.

The infusion method described above is the best mode currently known by the inventors for implementing the invention. Other possible methods for administering the secretin hormone, or a synthetic thereof, may be developed which may prove effective in implementing the invention, including, without limitation, sublingual administration (drops under the tongue) and transdermal administration (such as using a skin patch).

METHOD OF ACTION

Without intending to be bound by any theory, the inventors believe that: (i) the underlying cause of the neurochemical imbalance that results in ADD is metabolic in nature, and is caused, at least in large measure, by inefficiencies in the digestive system; and (ii) the mechanism of action in treating ADD individuals with the hormone secretin, or an acceptable pharmaceutical synthetic thereof, centers around the ability of the hormone to improve the efficiency of the digestive system, thereby resulting in more effective digestion and absorption of nutrients required for the synthesis of neurotransmitters necessary for proper brain function.

The dozen or so of the major neurotransmitters, and precursors to neurotransmitters, in the brain are made from amino acids. Amino acids are the chemical building blocks of protein molecules such as neurotransmitters, hormones and enzymes. Three of the main neurotransmitters, serotonin, dopamine and norepinephrine, are each made from one specific amino acid. There are approximately 29 amino acids, 20 of which serve as the building blocks of proteins in humans. Many of these amino acids are referred to as "nonessential," because

they can usually be made in the body as needed. The remaining amino acids are referred to as "essential," because the body cannot make them; they must be taken in from the diet.

Until the late 1960's, neuroscientists assumed that the brains supply of its neurotransmitters was controlled by the brain, independently of dietary or blood levels of the precursor nutrients, or amino acids, needed to make neurotransmitters. It was later discovered that the level of neurotransmitter precursor nutrients contained in a meal could directly affect the synthesis of neurotransmitters in the brain. However, the inventors believe that obtaining the requisite essential amino acids from the diet is not enough alone to create balanced neurotransmitters or brain chemicals. An individuals digestive system must be in sufficient working order to break down the dietary protein into individual amino acids so that the amino acids can be properly metabolized into a balanced supply of neurotransmitters and precursors to neurotransmitters. The inventors believe that many factors contribute to impair the efficiency of the digestive system, thereby creating a deficiency or imbalance in amino acids, including inherited disorders, environmental pollution, agricultural pesticides, processed foods, hormones and drugs from meat sources, and personal habits such as smoking.

Based on the therapeutic results achieved by treating ADD patients with the hormone secretin, it appears that the infusion of the hormone improves the body's digestive processes and synthesis of amino acids by activating certain digestive or metabolic processes that are dormant to some degree in the ADD individual. It is not likely that the one-time inundation of

the digestive system with the secretin hormone is sufficient, in and of itself, to effect the long term improvement in the body's ability to metabolize and synthesize nutrients into balanced neurotransmitters. It appears more likely that the infusion of significant quantities of secretin into the bloodstream serves to activate certain digestive or metabolic processes that lay dormant to some degree in the ADD individual, and that these enlivened processes are responsible for improving, either directly or indirectly, the breakdown of proteins and the synthesis of individual amino acids into balanced neurotransmitters. Because the previously dormant digestive or metabolic processes have been awakened, the body's enhanced ability to metabolize and synthesize the amino acids continues long after the infusion has been administered.

EXAMPLE I

A 40 year old male patient showed the following symptoms: distractibility, impulsivity, periodic mental fatigue and confusion (especially after engaging in tasks requiring sustained mental concentration), low stress tolerance with emotional over-reaction to the stress, poor organization with poor task completion and excessive temper. The patient was diagnosed as suffering from ADD. The patient was treated by administering two infusions of the hormone secretion, with the second infusion taking place three months following the first infusion. A few weeks after the first infusion, it was determined that the patients cognitive performance and his ability to handle stress noticeably improved. The patient noticed a considerable improvement in mental activities, in

particular the ability to complete tasks requiring mental concentration. The patient also noticed a substantial improvement in his temperament. Further improvement in mental functioning, task completion and temperament was observed after the second infusion. No adverse side-effects were observed nor did the patient complain of any.

EXAMPLE II

A 15 year old male patient showed the following symptoms: distractibility, impulsivity, difficulty in following directions, periodic mental fatigue (especially after engaging in tasks requiring sustained mental concentration), low stress tolerance, poor organization with poor task completion, easily frustrated, periodic depression, and difficulty in falling asleep and waking up. The patient was diagnosed as suffering from ADD. The patient was treated by administering a one-time infusion of the hormone secretion. Within one week after the treatment, the patient demonstrated an improvement in his ability to concentrate, follow directions and perform tasks requiring sustained mental effort. The patient also demonstrated higher stress tolerance, with less frustration. Moreover, the patient reported that he felt much more energetic, both mentally and physically, and that he experienced much improvement with his sleep patterns. No adverse side-effects were observed nor did the patient complain of any.

Due to the improvement in neurotransmitter synthesis and neuronal activity demonstrated by the use of the treatment method with ADD patients, the inventors believe that the

treatment method would also prove beneficial in treating other nervous system disorders (including other disorders which are associated with neurotransmitter system dysfunction), such as dyslexia, chronic fatigue syndrome, Parkinson's disease and Alzheimer disease.

What is claimed is:

1) A method for treating a patient diagnosed with Attention Deficit Disorder comprising an administration of an effective amount of secretin to the patient.

2) The Method of Claim 1 wherein the secretin dosage is about 1 Clinical Unit per pound of body weight.

3) The Method of Claim 1 wherein the secretin is administered by means selected from the group comprising intravenous, sublingual, and transdermal.

4) The Method of Claim 1 wherein the secretin dosage is administered over a period of about 1 to 4 minutes.

5) The Method of Claim 1 wherein the first 1 ml of secretin is administered over a period of about 1 minute, a pause of a period of about 1 minute is taken to observe for side effects, and the remainder of the solution is administered over a period of about 2 minutes to about 3 minutes.

6) The Method of Claim 2 wherein the secretin is administered by means selected from the group comprising intravenous, sublingual, and transdermal.

7) The Method of Claim 2 wherein the secretin dosage is administered over a period of about 1 to 4 minutes.

8) The Method of Claim 2 wherein the first 1 ml of the secretin dosage is administered over a period of about 1 minute, a pause of a period of about 1 minute is taken to observe for side effects, and the remainder of the dosage is administered over a period of about 2 minutes to about 3 minutes.

9) A method for treating a patient diagnosed with Attention Deficit Disorder comprising an administration of an effective amount of a pharmaceutical synthetic of secretin to the patient.

10) The Method of Claim 9 wherein the secretin dosage is about 1 Clinical Unit per pound of body weight.

11) The Method of Claim 9 wherein the secretin is administered by means selected from the group comprising intravenous, sublingual, and transdermal.

12) The Method of Claim 9 wherein the secretin dosage is administered over a period of about 1 to 4 minutes.

13) The Method of Claim 9 wherein the first 1 ml of secretin is administered over a period of about 1 minute, a pause of a period of about 1 minute is taken to observe for side effects, and the remainder of the solution is administered over a period of about 2 minutes to about 3 minutes.

14) A pharmaceutical composition in dosage form for administration to a subject comprising an effective amount of

secretin for treatment of Attention Deficit Disorder.

15) The invention of Claim 14 wherein the secretin dosage is administered over a period of about 1 to 4 minutes.

16) The invention of Claim 14 wherein the first 1 ml of the secretin dosage is administered over a period of 1 minute, a pause of a period of 1 minute is taken to observe for side effects, and the remainder of the dosage is administered over a period of about 2 minutes to about 3 minutes.

17) The invention of Claim 15 wherein the secretin dosage is 1 Clinical Unit per pound of body weight.

18) The invention of Claim 16 wherein the secretin dosage is 1 Clinical Unit per pound of body weight.

19) The method of Claim 13 wherein the procedure is repeated periodically as clinically necessary.

20) The method of Claim 8 wherein the procedure is repeated periodically as clinically necessary.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/31786

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 9/00, 38/00, 38/22; A61M 37/00; A61P 1/00, 25/00
US CL :514/2, 12; 424/423, 435, 449
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 99/64059 A2 (REPLIGEN CORPORATION) 16 December 1999, abstract, page 2, lines 12-22, page 3, lines 8-11, claims 1, 2, 3, 4, 5, 11, 12, 22.	1-3, 6, 9-11, 14, 17-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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